

RETINAL AND CONJUNCTIVAL VASCULAR CHANGES IN NORMAL AND TOXEMIC PREGNANCY*

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ADDITIONAL evidence has now accumulated indicating that there are changes in the peripheral vascular bed, both in normal and toxemic pregnancy.^{1, 2} Initial observations of the arterioles in toxemia date back a century. Soon after the discovery of the ophthalmoscope, retinal detachment associated with toxemia,³ was described in 1856. From 1895 to 1924 various authors reported the presence of retinal hemorrhages and transudates in the toxemias of pregnancy.^{4, 5} They were all aware that such findings indicated a poor prognosis for the infant, with a survival rate of approximately 25 per cent. Volhard in 1921⁶ was responsible for the theory that these retinal changes resulted from arteriolar spasm which produced areas of ischemia and secondary hemorrhage. Prior to that date, the general impression was that the retinal abnormalities were related to renal disease and associated albuminuria.⁷ In 1928 Haselhorst and Mylius⁸ clearly recognized the presence of localized and diffuse arteriolar spasm which was reversible in eclampsia. Since that time in this country numerous reports have confirmed the arteriolar changes that occur in toxemia of pregnancy (Mussey and Mundell,⁹ Wagener and Keith,¹⁰ and Hallum¹¹).

Retinal hemorrhages in vomiting of pregnancy were first discovered by Stander,¹² and Tillman¹³ in 1932 and 1934 respectively. A summary of this state by Schjøtt-Rivers¹⁴ indicated the importance of extensive retinal hemorrhage associated with vomiting of pregnancy. Failure to interrupt the pregnancy in many instances resulted in maternal death. At the present time, probably related to improved methods of parenteral feeding, retinal hemorrhages in vomiting of pregnancy are almost un-

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known. Rare fine "splinter" hemorrhages¹⁵ have been noted during a severe episode of vomiting, and then have been seen to disappear after commencement of intravenous feeding.

During normal pregnancy, no observable variations have been seen in retinal arterioles and venules. In mild pre-eclampsia minimal changes or early mild spasm have been noted, whereas in severe pre-eclampsia, more advanced retinal changes occur. Increasing spasm usually is indicative of a further advancement in the toxemic process. However, any reduction in the spasm associated with severe pre-eclampsia does not necessarily mean improvement of the toxemic state. At times, a sudden decrease in arteriolar spasm may suggest early fetal death. Retinal hemorrhages and transudates are extremely rare in acute toxemia. Their presence indicates interruption of pregnancy to preserve maternal vision, and continuation of pregnancy will probably not improve the fetal survival rate. In our experience the presence of retinal hemorrhages in acute toxemia is associated with a 33 per cent fetal mortality rate. The early onset of eclampsia is usually concomitant with the more advanced retinal findings. Acute eclampsia in the final weeks of pregnancy is generally associated with severe reversible arteriolar spasm. In this late type of eclampsia, there is ordinarily no silver wire appearance or evidence of arteriovenular compression. The presence of a hydatidiform mole in the second trimester of pregnancy is on occasion associated with advanced arteriolar spasm. Such vascular phenomenon in the second trimester, unassociated with known hypertensive disease, suggests the presence of a mole.

Ophthalmoscopy is most useful in the diagnosis of severe essential hypertension.¹⁶ Evaluation of essential hypertension prior to, or early in pregnancy, to determine the chances of a successful outcome, should always include bilateral retinal observations. The presence of Grade II spasm, old hemorrhages, transudates, and silver wiring of the vessels indicates a poor prognosis for a living infant. If retinal hemorrhages are evident, pregnancy is contraindicated and therapeutic abortion should be performed.

In benign hypertension with a blood pressure elevation at moderate levels (diastolic pressure of 90 to 109), minimal retinal arteriolar changes may be observed. If superimposition of toxemia does not occur, retinal observations are only of use as a baseline for the evaluation of later changes. In severe hypertension, in which the diastolic pressure is above



* Fig. 1—M.S. shows marked local arteriolar spasm (arrow) and Grade II changes (three weeks before delivery).

110 mm. Hg, the retinal arterioles contribute important information for fetal prognosis, and may indicate further exacerbation of the toxemic process. If albuminuria and severe hypertension are associated with Grade II retinal arteriolar changes (severe local and generalized spasm), fetal growth usually ceases and intrauterine death may be anticipated in an average of three weeks after the onset of superimposition.

Case 1. M.S. (No. 197999), a forty-one-year-old para 0, gravida ii, was admitted in 1948 because of an increase in hypertension to 170/110 during the twenty-ninth week of pregnancy. A previous pregnancy

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had terminated spontaneously at the twentieth week. No albuminuria or edema was present. Retinal vessels of Grade II, with severe local spasm and arteriovenous compression phenomena, were observed. By the thirty-third week the blood pressure had returned to the previously recorded mild hypertensive limits and the spasm in the eyes was noted to be decreased. However, the fetal heart was absent and one week later a 1330 gm. macerated infant was delivered. Renal function and blood uric acid levels were within normal limits. The blood pressure decreased to 140/90 and retinal spasm subsided one week prior to delivery, which was probably the time of fetal death. Nine months postpartum blood pressure was 180/120 without clinical symptoms. Figure 1 shows the Grade II retinal arteriolar spasm. The exacerbation of blood pressure in the twenty-ninth week of pregnancy and Grade II retinal changes were followed rapidly by fetal death. The improvement in the retinal vascular picture with an associated drop in blood pressure occurred soon after the infant's death. These ophthalmological observations of the retina, as well as those of the other cases presented, have been made by a member of the Ophthalmology Department of Cornell University Medical College. The accuracy of classification of retinal findings improves when only one examiner is responsible for all the observations. Similar experience has been noted by Dieckmann.¹⁷

The presence of Grade III changes in the retinal vessels associated with essential hypertension is a serious complication in patients whom we have followed. Hemorrhages and transudates associated with essential hypertension usually result in a 75 per cent infant mortality. It is common, following the interruption of such a pregnancy, for most of the hemorrhages and transudates to disappear spontaneously with the subsidence of the toxemic process.

Case 2. E.F. (No. 137025), a forty-two-year-old para viii, gravida xii, with seven living children, was admitted in the thirty-fourth week of pregnancy because of hypertension (170/105). She was first seen in 1936 for severe pre-eclampsia complicated by premature separation of the placenta, and she subsequently delivered a stillborn infant of 3830 gm. In 1940 a pregnancy was again complicated by severe hypertension, the blood pressure reaching a level of 180/120. Following a term delivery the blood pressure was 145/115. The patient was advised against future pregnancies and a tubal sterilization was suggested, but she refused. She was seen during the present pregnancy on the day prior to



Fig. 2—E.F. shows Grade III changes with local spasm, hemorrhages, and transudates. Carbon arc spot adjoins disc at 11:30 (sixteen hours before cesarean section).

admission, when the urine showed a 4 plus albumin. The eye grounds showed copper and silver wire arterioles with local and generalized spasm and transudates, and were classified as Grade III (Fig. 2). A low flap cesarean section and tubal sterilization were performed and a healthy 2820 gm. infant was delivered. Blood pressure at the time of section was 190/120 and ten days postpartum it was 165/100. The final diagnosis was severe hypertension with superimposed pre-eclampsia. There was some reduction of renal function postpartum. It was fortunate in this case to obtain a living infant.

The baby of the diabetic mother is in general larger than the average.¹⁸ However, when diabetic retinopathy occurs, a normal or smaller than average size infant is the rule. Diabetic retinopathy¹⁹ is characterized in general by small yellowish transudates and deep hemorrhages in the macula area, and small superficial hemorrhages around the disc. The following case illustrates this process.

Case 3. J.L. (No. 550616), a twenty-one-year-old para 0, gravida ii, with diabetes of fifteen years duration, was admitted to the hospital



Fig. 3—J.L. shows mixed diabetic retinopathy (arrow) in the left macular area. Carbon arc spot is above macula. Arterioles show only Grade I changes (five days before delivery).

in 1949 when twenty-four weeks pregnant, because of diabetic retinopathy (transudate and hemorrhages). The blood pressure was 140/90, there was a 3 plus albuminuria, and renal function tests showed a significant impairment. Because of her extreme desire for the infant, the pregnancy was not interrupted. Daily requirements of insulin consisted of 50 units. In the thirty-third week, because of increased generalized edema, excessive weight gain, and progressive retinopathy, a cesarean section was performed. The infant weighed 1490 mg. and died twenty-four hours later. Postmortem examination showed nothing significant except immaturity. Figure 3 illustrates the diabetic retinopathy with perimacular transudates and hemorrhages.

The early onset of diabetic retinopathy with extension during pregnancy will usually result in multiple scotomata and reduction in vision. If this diabetic retinopathy is extensive in early pregnancy, prognosis for a live infant is usually hopeless. After pregnancy, diabetic retino-

pathy tends to subside and may completely disappear. If, however, the process is extensive, permanent loss of vision may result.

Careful observation of diabetic pregnant women without toxemia has demonstrated no significant changes in the conjunctival vascular bed. This is at variance to a recent report by Ditzel and Sagild²⁰ who show numerous forms of conjunctival changes. In diabetes associated with toxemia of pregnancy, the conjunctival vessels show similar findings as in other patients with toxemia. Any minor variations in the diabetic are of more significance with the known higher fetal mortality rate in toxemia.

If chronic nephritis is associated with retinal arteriolar changes, the prognosis for a living infant is poor. On the other hand, if albuminuria is present with good renal function and normal retinal vessels, the outlook for a live infant is good. When extensive renal disease is evident, essential hypertension is almost invariably associated with marked retinal arteriolar variations of Grade II or more. This combination should contraindicate pregnancy because of the hopeless prognosis for a live infant and the usually short duration of maternal life. If the diagnosis of renal disease is made late in pregnancy the absence of retinal abnormalities is a good sign for the infant, whereas extensive retinal involvement will usually be associated with reduced fetal growth and intrauterine death.

In view of recent pathological evidence furnished by Hertig,²¹ Sheehan,²² and Falkiner,²³ that toxemias of pregnancy are associated with lesions of the smaller arterioles, it was considered important to observe the peripheral vascular bed in vivo. Observations of finer vessels of the nail bed have been described by several investigators.^{24, 25} These vessels, however, appear to represent arteriovenous shunts²⁶ and are not typical, anatomically, of the peripheral vascular bed. Photographs of these vessels have been unsatisfactory. Following the fundamental work of Lee and Holze²⁷ on the bulbar conjunctival vessels, a series of normal and toxemic pregnancies was observed, and representative photographs of the vessels were taken by means of a slit-lamp microscope and an attached 35 mm. camera. In normal pregnancy, there are gradual changes in the vascular pattern and in the characteristics of flow. In the first trimester, the arteriolar flow is very rapid, the venules are filled, and the capillary bed is clearly visualized. After the twentieth week, there is a gradual reduction in the rate of blood flow. This slow-

ing appears maximum several weeks before labor, during labor, and in the first three days postpartum. Concomitantly with the reduction in the flow rate, there is the appearance of granularity in the venules which was formerly described as sludge by Knisely and his coworkers.²⁸ This granularity reaches a peak at about the same time that the reduction in flow rate is at a maximum. We believe that this granularity is directly associated with the rate of blood flow and is not related to the cohesion of red blood cells. Changes in plasma protein,^{29, 30} manifested by an increase in globulin and a reduction in albumin, may be partly responsible for the granular appearance. Granularity may be very extensive at the time of labor and so far as we could determine, is a normal variant in pregnancy. Ischemia of the capillary bed is an important alteration in the vessel pattern seen during pregnancy. As term is approached, the number of capillaries visualized gradually becomes reduced; this may be seen without the microscope, by directly observing the bulbar conjunctiva late in pregnancy. In toxemia this ischemia is more prominent. In severe pre-eclampsia and eclampsia, localized areas of the capillary bed in the bulbar conjunctiva for all practical purposes, may be completely absent. This phenomenon is clearly illustrated in the following case.

Case 4. U.A. (No. 664007). This eighteen-year-old primigravida was admitted to the hospital in the thirty-eighth week of pregnancy because of sudden elevation in blood pressure to 150/110, 4 plus albuminuria, and severe headache. On the day following admission the blood pressure rose to 190/120. The membranes were ruptured and during pitocin induction a generalized convulsion occurred. Several hours later a normal healthy 2340 gm. infant was delivered. Two other convulsions occurred immediately following the delivery. At this time, retinal vessels demonstrated a Grade I plus change with mild peripheral attenuation. Conjunctival observations indicated a complete absence of any functioning capillaries. On the sixth postpartum day, the arterioles showed incomplete filling, indicating spasm and profound ischemia of the capillary bed (Fig. 4). Eight days postpartum there was no retinal spasm remaining, and the peripheral attenuation disappeared. At two months postpartum there was a return to a normal conjunctival pattern (Fig. 5).

In the first six months of normal pregnancy, there is no evident arteriolar spasm in the conjunctival vessels. Vasomotion, which is a fine

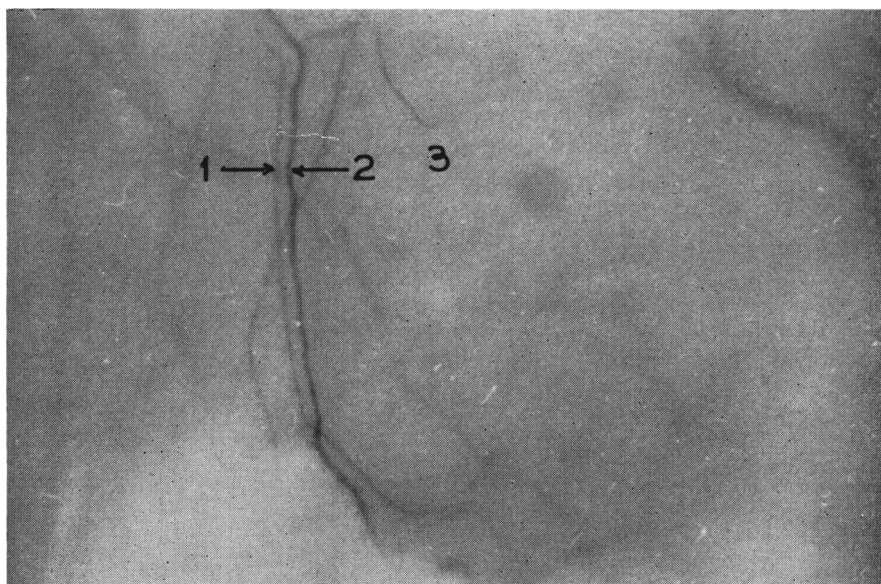


Fig. 4—U.A. Eclampsia. Six days postpartum.
1—Arteriole—Grade II spasm
2—Venule
3—Capillary bed—Grade III ischemia

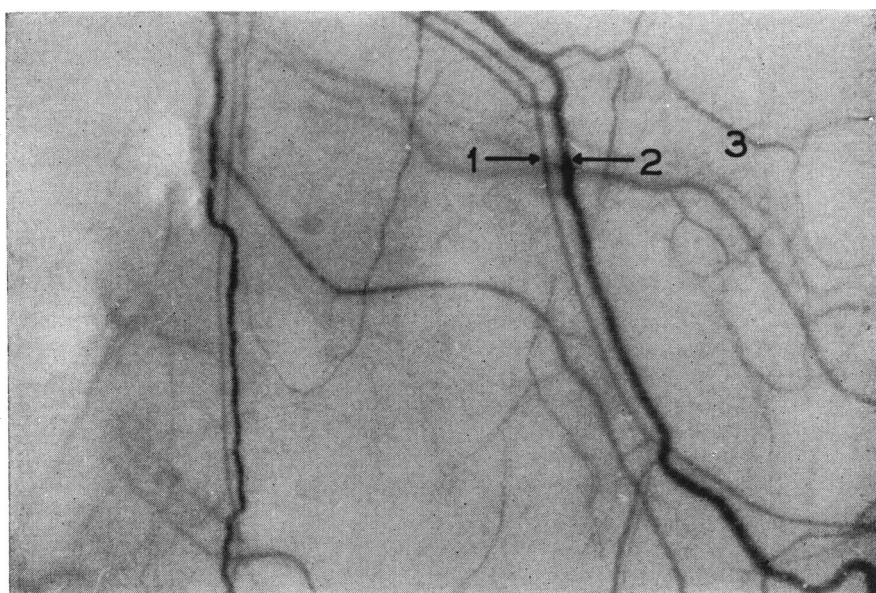


Fig. 5—U.A. Eclampsia. Two months postpartum.
1—Arteriole—Grade O-I spasm
2—Venule
3—Capillary bed—normal

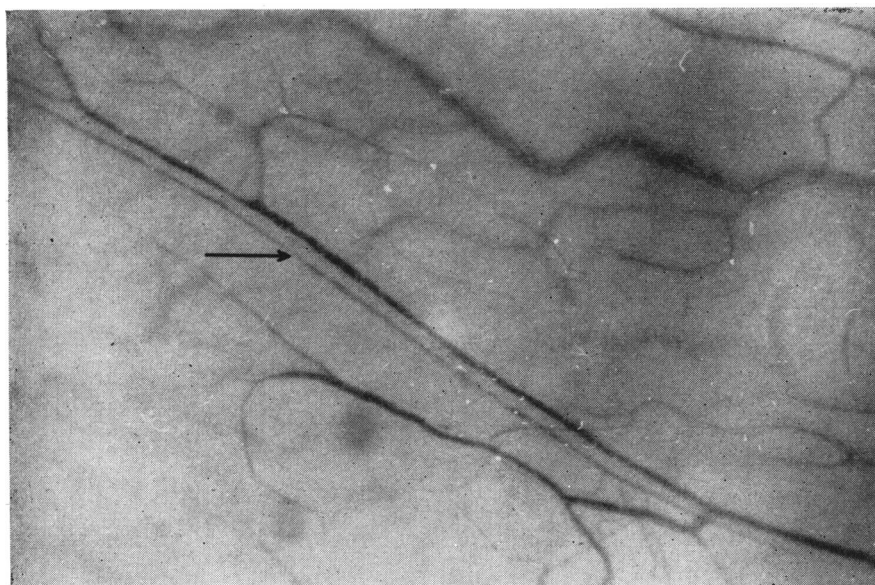


Fig. 6—S.R. 489005. Severe pre-eclampsia. One week prior to fetal death in utero. Grade II spasm.

wave-like activity, may be seen in these vessels. In 20 per cent of the normal, a mild spasm may be noted in the last trimester, during labor, and in the first week postpartum. Any further spasm, Grade II or over, indicates an abnormal process, and is associated with the toxemias. The period of pregnancy, in which the spasm is first noted, may be significant. The presence of moderate spasm in the first trimester is indicative of hypertensive disease, whereas, if it is seen during the course of labor, it may be a part of the normal process. The presence of ischemia is related to the extent of the spasm. In toxemias that occur late in pregnancy, the arterioles become extremely attenuated and are thinned out due to generalized hypertonicity of the vessel wall. Bulbs and areas of spasm are not discernible because of incomplete filling of the vessels. In instances of eclampsia, areas of the conjunctiva show complete blanching with only occasional venules being present. In the following case extensive localized spasm is illustrated in severe pre-eclampsia (Fig. 6).

Case 5. S.R. (No. 489005). This thirty-two year old para iv gravida iv was admitted in the thirty-first week of pregnancy with severe

pre-eclampsia, elevated blood pressure of 150/105, and 4 plus albuminuria. Retinal and conjunctival vessels showed a Grade II arteriolar spasm. In the thirty-sixth week pitocin induction was used to efface the cervix. During the third day of pitocin induction fetal distress was noted and a fetal heart rate of 80 was recorded. When the pitocin was discontinued, the fetal heart returned to normal. Later the same day, because of the small size of the fetus, pitocin was readministered and the fetal heart was lost. The patient delivered a 1410 gm. deadborn in the thirty-seventh week of pregnancy. Urea clearance, blood area nitrogen, and concentration tests were normal.

Tortuosity of the capillary bed is not influenced by normal pregnancy. In approximately 30 per cent of the more advanced instances of essential hypertension, extensive corkscrew-like elongations of the capillaries have been observed. It is our impression that this finding usually indicates vascular disease. In one hundred normal patients studied during pregnancy, extensive tortuosity as described above was not present.

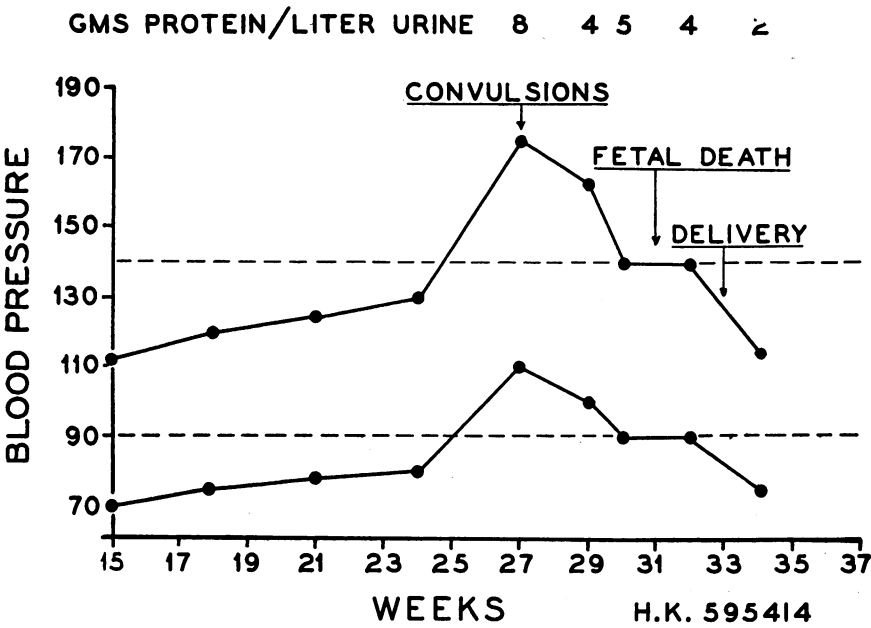
Case 6. H.K. (No. 595414). This twenty-four year old primigravida suddenly developed convulsions in the twenty-seventh week of pregnancy. Prior to this date blood pressure, urinalysis, and weight gain were within normal limits. After three convulsions she was admitted to the hospital. The blood pressure at this time was 174/112, albuminuria was 4 plus, and there was generalized edema. She was given intravenous pentothal and was fully digitalized. Chemical examination of the blood showed a uric acid of 5.0 mg. per cent, total proteins 4.6, albumin 3.7, globulin 1.1 and urinary non-protein nitrogen 34.0. Urinary output was adequate. Ophthalmoscopy showed several areas of moderate local spasm and generalized mild spasm. No hemorrhages or exudates were visualized and the diagnosis was Grade II arteriolar change.

No further convulsions occurred, and the blood pressure receded to border-line levels. However, there were occasional severe frontal headaches and albuminuria persisted, ranging from 3.0 to 8.0 gm. per liter. Frequent measurements of the uterine fundus over a six weeks' period revealed no growth. Retinal observations showed some improvement in the spasm, body edema disappeared, and weight remained stationary. Five weeks after admission, in the thirty-second week, the fetal heart was lost, and one week later a 1000 gm. deadborn infant was delivered. The urea clearance and concentration tests were normal. After ten days



Fig. 7—H.K. Eclampsia. Postpartum. Grade III tortuosity.
1—Arteriole 2—Venule 3—Capillary

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postpartum the blood pressure and retinal alterations returned to normal (Fig. 7). Following this pregnancy she was observed for approximately two years during which time blood pressure was within normal range. A second pregnancy two years later was complicated by severe pre-eclampsia; hospitalization was required and a living infant resulted. Chart 1 shows the clinical course, onset of convulsions, and the time of fetal death. Although the blood pressure returned to normal, and there was some improvement in both retinal and conjunctival vessels, intrauterine death occurred six weeks following the convulsions. In spite of some general improvement, continuation of the toxemic state was indicated by the lack of uterine growth.

Certain other unusual features have been observed in the study of the conjunctival vascular bed in toxemia, which are further evidence of peripheral vascular alterations. In two instances of severe essential hypertension, aneurysmal dilatations of the deep scleral veins have been noted. In four cases thrombi have been seen in acute toxemia and have faded in the first week postpartum. In five patients true conjunctival petechial hemorrhages have been visualized.

SUMMARY

Page,³⁰ in his recent monograph on the toxemias of pregnancy, indicates the importance of the arteriolar spasm associated with this disease. Irving³¹ and Eastman³² related some years ago the evidence for the presence of this vascular phenomenon associated with the toxemias. McCall³³ in his study of cerebral circulation, has demonstrated reduced blood flow and increased intravascular resistance in eclampsia. At present, it has not been possible to observe directly the terminal circulation of the placental bed in pregnancy. The total circulating blood to the uterus is probably reduced in acute toxemia and severe essential hypertension.³⁴ The only satisfactory areas that are at present available in the human for the study of the peripheral vascular bed are the retina and conjunctiva. It is our belief that the vascular pattern we have described is mediated by some chemical factor from the uteroplacental bed which produces the vascular spasm in the eye vessels and probably in other organs of the body. The conjunctival changes in normal pregnancy graduate into abnormal toxemic findings. This suggests that there is no clear cut dividing line between true toxemia and normal pregnancy. These variations of retinal and conjunctival circulations are additional

factors which may be used to evaluate the severity of the disease process and to further our understanding of peripheral vascular phenomena in normal and abnormal pregnancy.

CONCLUSIONS

1. The vessels of the eye (retina and bulbar conjunctiva) undergo various changes in the toxemias of pregnancy. Some of these alterations are important in evaluating the severity of the toxic process and in furthering our understanding of this disease entity.

2. In vomiting of pregnancy retinal hemorrhages are no longer seen, probably because of improved methods in nutrition.

3. In acute toxemia severe spasm indicates an advancement of the disease process with an increasing danger of intrauterine fetal death.

4. In the non-pregnant individual or in the first trimester, retinal observations are valuable in determining the presence and extent of the vascular disease and the probability of a successful fetal outcome.

5. The presence of retinal hemorrhages and transudates is associated with high fetal mortality in both the acute and hypertensive toxemias and indicates early interruption of pregnancy.

6. Diabetic retinopathy is a serious complication which is associated with reduced growth of the fetus and maternal renal disease; it may result in permanent loss of maternal vision.

7. Variations in the peripheral vascular bed of the bulbar conjunctiva occur in normal pregnancy. Further progression of these changes is evident in the toxemias.

8. Advancing arteriolar spasm of the conjunctiva is significant as a prognostic sign in toxemia. Increasing ischemia develops in severe toxemia and reaches a maximum in eclampsia.

9. The presence of diffuse capillary tortuosity suggests underlying essential hypertension.

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